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Effects of SGLT2 inhibitors on fractures and bone mineral density in type 2 diabetes: An updated meta-analysis

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Abstract

Background: The aim of the study is to update and determine the effects of sodium glucose cotransporter 2 (SGLT2) inhibitor therapy on fracture and bone mineral density (BMD) in patients with type 2 diabetes mellitus (T2DM).

Methods: We identified 27 eligible randomized controlled trials (RCTs) that compared the efficacy and safety of SGLT2 inhibitors to a placebo in 20 895 T2DM participants, with an average duration of 64.22 weeks. The relative risk (RR) of bone fracture and weighted mean difference (WMD) of changes in the BMD from baseline were determined to evaluate the risk of fracture. The degree of heterogeneity was evaluated by the I^2 statistic, and publication bias was estimated using a funnel plot and Egger test.

Results: The pooled RR was 1.02 (95% CI [0.81, 1.28]) with low heterogeneity, indicating that SGLT2 inhibitor treatment was not correlated with a higher risk of fracture. Additionally, no increased risk was found for patients with different ages, sexes, and levels of HbA1c and some biochemical indicators. Three trials with 1303 patients reported a change in the BMD from baseline. SGLT2 inhibitor treatment did not decrease the BMD at four skeletal sites (lumbar spine, femoral neck, total hip, and distal forearm), and the overall WMD was 0.08 (95% CI [−0.09, 0.26]). No significant publication bias was detected.

Conclusions: No increased risk for bone fracture was detected in patients with T2DM treated with SGLT2 inhibitors in this meta-analysis. SGLT2 inhibitor therapy did not appear to affect bone health, but more long-term detailed data are needed to validate this conclusion.

KEYWORDS

bone mineral density, fracture, meta-analysis, sodium glucose cotransporter 2, type 2 diabetes mellitus

1 | INTRODUCTION

Diabetes mellitus (DM) is a global public health problem. In 2017, 8.8% adults 20 to 79 years of age suffered from DM. Following this trend, approximately 629 million people 20 to 79 years of age will have DM by 2045.[1] Currently, several therapies are available for type 2 diabetes mellitus (T2DM), including metformin (MET), sulfonylurea (SU), thiazolidinedione (TZD), α-glucosidase inhibitors (AGIs), dipeptidyl peptidase IV (DPP4) inhibitors, and insulin, but these therapies have common side effects that cannot be ignored.[2]

Sodium glucose cotransporter 2 (SGLT2) inhibitors are a class of novel hypoglycaemic drug that alters calcium and phosphate homeostasis and acts on the kidneys to promote urinary glucose excretion, thereby decreasing the plasma glucose level.[3] Many drugs belong to the SGLT2 inhibitors, including dapagliflozin, canagliflozin, empagliflozin, ertugliflozin, ipragliflozin, tofogliflozin, and luseogliflozin. Physiologically, SGLT2 and sodium glucose cotransporter 1 (SGLT1) together reabsorb filtered glucose, with the former accounting for the majority of this function (80%-90%). In patients with poorly controlled T2DM, the kidneys improve the threshold of glucosuria and reabsorb more glucose, resulting in an increase in the maximum glucose reabsorptive capacity (Tm_G). Accordingly, SGLT2 inhibitors can reduce the threshold of glucosuria and Tm_G, decrease reabsorption, and alleviate glucotoxicity.[3]

SGLT2 inhibitors have been proven to have protective effects on the blood pressure (BP), cardiovascular issues,[4] lipid spectrum, and body weight.[3] Inevitably, SGLT2 inhibitors also have numerous safety problems. Genital infections, urinary tract infections, and reduced intravascular volume–related diseases appear to be the major adverse reactions to SGLT2 inhibitor therapy. In addition, equal importance should be attached to hyperkalaemia for canagliflozin and bladder cancer for dapagliflozin.[3]

In 2014, Kohan et al[5] reported a clinical trial of 252 patients with inadequately controlled T2DM and moderate renal impairment. Bone fracture events occurred in five patients receiving 5 mg/day of dapagliflozin, eight patients receiving 10 mg/day of dapagliflozin, and no patient receiving the placebo. An increased bone fracture risk was also detected in canagliflozin-treated patients who were older, had cardiovascular diseases, and had a lower baseline estimated glomerular filtration rate (eGFR) and higher baseline diuretic use.[6] In particular, it has been well demonstrated that several antidiabetic agents can impair the bone health[7] in addition to the negative effect of diabetes itself to the skeleton.[8] However, a large number of trials have shown different results for canagliflozin, dapagliflozin, and empagliflozin; SGLT2 inhibitors do not affect bone health.[9-11] Kohler et al reported that the incidence of bone fracture was similar between the empagliflozin and placebo treatment groups and even within renal function (eGFR) subgroups.[12] Two meta-analyses that previously reviewed trials on SGLT2 inhibitors together with bone fractures reported that evidence of an association was lacking.[13,14] In general, whether SGLT2 inhibitors can increase the risk of bone fractures is debatable and needs further discussion.[15] Newer, larger sample and longer term studies with relatively complete data need to be included, and the preliminary conclusion needs to be updated.[15,16] For this purpose, we once again reviewed trials on SGLT2 inhibitors to reach a more comprehensive and reliable conclusion.

2 | MATERIALS AND METHODS

This meta-analysis was performed based on the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[17]

2.1 | Search strategy

A comprehensive literature search was conducted with the PubMed, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) databases and ClinicalTrials.gov from inception to March 2018. The search key terms were as follows: "Sodium glucose cotransporter 2 inhibitors" or "SGLT2 inhibitors" or corresponding variants, "randomized controlled trial (RCT)", and the names of 11 individual SGLT2 inhibitors (dapagliflozin, canagliflozin, empagliflozin, ertugliflozin, tofogliflozin, luseogliflozin, ipragliflozin, sotagliflozin, remogliflozin, and sergliflozin). Articles in English or Chinese were included. Then, we manually searched published and unpublished trials in the relevant meta-analyses and at ClinicalTrials.gov (https://clinicaltrials.gov/). The detailed search strategy is outlined in Appendix 1.

2.2 | Eligibility criteria

Trials were included according to the following criteria: (1) participants, patients with T2DM; (2) intervention, SGLT2 inhibitor therapy; (3) comparison, placebo therapy; (4) outcome, incidence of bone fractures or a change in the bone mineral density (BMD) from baseline; and (5) study, randomized controlled trials (RCTs) extending at least 24 weeks. We excluded pooled analyses, non-RCTs, trials with a duration less than 24 weeks, and studies on patients with type 1 diabetes mellitus (T1DM) or healthy volunteers.

2.3 | Data extraction

Two reviewers independently extracted the relevant data. The data were abstracted as follows: (1) first author name; (2) publication year; (3) clinical trial number; (4) populations; (5) trial duration; (6) background therapies; (7) baseline characteristics of the participants, including the mean age, proportion of men, mean duration of T2DM, mean glycosylated haemoglobin A1c (HbA1c), and mean body mass index (BMI); (8) type and dosage of SGLT2 inhibitors; and (9) incidence of bone fracture and changes in BMD from baseline. Discrepancies were settled by consensus between the two reviewers or by a senior reviewer referral.

2.4 | Quality assessment

We used the Cochrane Risk of Bias Tool to assess the quality of the trials.[18] Two reviewers independently judged each section as low risk, unclear risk, and high risk of bias. Publication bias was visually inspected using a funnel plot and assessed by Egger test.[19]

2.5 | Statistical analysis

We chose the pooled relative risk (RR) and 95% confidence interval (CI) to evaluate the correlation between SGLT2 inhibitor intake and the risk of bone fractures and chose the weighted mean difference (WMD) and

TABLE 1 Characteristics of included trials on sodium glucose cotransporter 2 (SGLT2) inhibitors and fractures

Clinical Trial No.	Author Year	Population	Trial Duration, wk	Background Therapy	Baseline characteristics					Control, n	Number of Fracture (C)	SGLT2 Inhibitors (n)	Number of Fracture (SGLT2i)
					Age, y	Male, %	HbA1c, %	BMI, kg/m^2	Duration of T2DM, y				
NCT02157298	Araki 2016[20]	Multicentre in Japan	52	INS	58.1 (9.8)	129 (70.8)	8.3 (0.8)	26.6 (4.5)	15.0 (9.0)	PLA (60)	0	DAP 5 mg (122)	3
NCT00528879	Bailey 2013[41]	Multicountry	102	MET	53. 9 (9.7)	292 (53.5)	8.1 (0.9)	31.5 (5.0)	6.1 (5.6)	PLA (137)	2	DAP 2.5 mg (137), 5 mg (137), 10 mg (135)	2, 2, 3
NCT01164501	Barnett 2014[32]	Multicountry	52	AHAs	63.9 (8.8)	430 (58.3)	8.0 (0.8)	30.7 (5.5)	NR	PLA (319)	12	EMP 10 mg (98), 25 mg (321)	2, 3
NCT01106651	Bode 2015[33]	Multicountry	104	AHAs	63.6 (6.2)	396 (55.5)	7.8 (0.8)	31.6 (4.6)	11.7 (7.5)	PLA (237)	5	CAN 100 mg (241), 300 mg (236)	7, 10
NCT00855166	Bolinder 2014[27]	Multicountry	102	MET	60.7 (7.6)	100 (54.9)	7.2 (0.5)	31.9 (3.9)	5.7 (4.9)	PLA (91)	1	DAP 10 mg (91)	1
NCT02036515	Dagogo-Jack 2017[42]	Multicountry	52	MET and SITA	59.1 (9.0)	263 (56.9)	8.0 (0.9)	30.8 (6.0)	9.5 (5.7)	PLA (153)	1	ERT 5 mg (156), 15 mg (153)	2, 2
NCT01986855	Grunberger 2017[34]	Multicountry	54	AHAs	67.2 (8.6)	231 (49.5)	8.2 (0.9)	32.5 (6.1)	14.2 (8.5)	PLA (154)	1	ERT 5 mg (158), 15 mg (155)	4, 0
NCT01159600	Häring 2014[43]	Multicountry	24	MET	55.7 (9.9)	361 (56.7)	7.9 (0.9)	29.2 (5.5)	NR	PLA (207)	0	EMP 10 mg (217), 25 mg (213)	3, 1
NCT02354235	Kadowaki 2017[22]	Multicentre in Japan	24	TENE	57.2 (9.2)	107 (77.5)	8.0 (0.9)	26.0 (4.0)	7.4 (6.2)	PLA (68)	0	CAN 100 mg (70)	1
NR	Kaku 2014[21]	Multicentre in Japan	24	NR	58.8 (9.8)	155 (59.4)	7.5 (0.7)	25.4 (4.3)	4.9 (5.4)	PLA (87)	0	DAP 5 mg (86), 10 mg (88)	0, 1
NR	Kaku 2017[10]	Multicountry	206	SU	61.0 (9.2)	1118 (73.7)	8.1 (0.8)	26.6 (4.0)	NR	PLA (511)	16	EMP 10 mg (505), 25 mg (501)	23, 12
NCT00663260	Kohan 2014[5]	Multicountry	104	AHAs	67.0 (8.4)	164 (65.1)	8.4 (1.1)	NR	16.9 (9.6)	PLA (84)	0	DAP 5 mg (83), 10 mg (85)	5, 8
NCT01042977	Leiter 2014[35]	Multicountry	52	AHAs	63.8 (7.3)	644 (66.9)	8.1 (0.8)	32.9 (5.5)	13.2 (8.3)	PLA (482)	8	DAP 10 mg (482)	5
NCT01505426	Lu 2016[23]	Multisite in Korea and China	24	MET	53.7 (11.3)	77 (64.7)	7.7 (0.7)	26.8 (5.9)	6.2 (5.0)	PLA (83)	1	IPR 50 mg (87)	0
NCT01646320	Mathieu 2015[44]	Multicountry	52	SAXA and MET	55.1 (9.1)	146 (45.6)	8.2 (1.0)	31.7 (5.0)	7.6 (6.1)	PLA (160)	2	DAP 10 mg (160)	0
NCT02226003	Miller 2018[45]	Multicountry	26	SITA	55.6 (9.9)	167 (57.4)	9.0 (0.9)	32.3 (6.1)	NR	PLA (97)	1	ERT 5 mg (98), 15 mg (96)	0, 0
NCT01106625[24]	NR	Multicountry	52	MET and SU	56.7 (9.3)	239 (51.0)	NR	NR	NR	PLA (156)	1	CAN 100 mg (157), 300 mg (156)	0, 0
NCT01032629	Neal 2015[11]	Multicountry	52	INS	62.7 (8.0)	1370 (66.1)	8.3 (0.9)	33.1 (6.4)	16.2 (7.5)	PLA (690)	11	CAN 100 mg (692), 300 mg (690)	18, 8
NCT01989754	Rodbard 2016[46]	Multicountry	26	MET and SITA	57.4 (9.7)	121 (56.8)	8.5 (0.9)	32.0 (5.6)	9.9 (5.7)	PLA (106)	1	CAN 100 to 300 mg (107)	0
NCT01177813	Roden 2013[36]	Multicountry	24	AHAs	55.0 (11.4)	410 (60.6)	7.9 (0.8)	28.4 (5.7)	NR	PLA (228)	0	EMP 10 mg (224), 25 mg (224)	0, 1
NCT01306214	Rosenstock 2014[47]	Multicountry	52	INS alone or plus MET	56.7 (9.5)	256 (45)	8.3 (0.7)	34.8 (4.1)	NR	PLA (188)	1	EMP 10 mg (186), 25 mg (189)	0, 0
NCT01011868	Rosenstock 2015[48]	Multicountry	78	INS	58.8 (9.9)	276 (55.9)	8.2 (0.8)	32.2 (5.9)	NR	PLA (170)	1	EMP 10 mg (169), 25 mg (155)	0,1
NCT02033889	Rosenstock 2017[49]	NR	104	MET	56.7 (8.7)	288 (46.4)	8.1 (0.9)	30.9 (4.7)	8.0 (6.0)	PLA (209)	1	ERT 5 mg (207), 15 mg (205)	1, 1
NCT01131676	Wanner 2018[50]	Multicountry	164	TENE	63.1 (8.6)	4973 (71.4)	8.1 (0.9)	30.6 (5.3)	NR	PLA (2333)	38	EMP 10 mg (2345), 25 mg (2340)	37, 35
NCT01064414	Yale 2014[37]	Multicountry	52	AHAs	68.5 (8.3)	163 (60.6)	8.0 (0.9)	33.0 (6.2)	16.3 (8.5)	PLA (90)	2	CAN 100 mg (90), 300 mg (89)	1, 1
NCT01032629	Yale 2017[51]	Multicountry	52	SU	64.8 (8.1)	120 (55.8)	8.3 (1.0)	29.4 (5.4)	9.2 (6.4)	PLA (69)	1	CAN 100 mg (74), 300 mg (72)	2, 3
NCT01095666	Yang 2015[52]	Multicountry	24	MET	53.7 (9.3)	241 (54.3)	8.1 (0.8)	26.1 (3.3)	4.9 (4.3)	PLA (145)	1	DAP 5 mg (147), 10 mg (152)	0, 2

Note. Data are mean (SD) unless otherwise indicated.

Abbreviations: HbA1c, glycated haemoglobin A1c; BMI, body mass index; T2DM, type 2 diabetes mellitus; SGLT2i, sodium glucose cotransporter 2 inhibitors; NR, not reported; PLA, placebo; DAP, dapagliflozin; CAN, canagliflozin; ERT, ertugliflozin; EMP, empagliflozin; IPR, ipragliflozin; MET, metformin; SITA, sitagliptin; SAXA, saxagliptin; TENE, teneligliptin; SU, sulfonylurea; AHAs, antihyperglycaemic agents.

95% CI for the correlation between SGLT2 inhibitor therapy and reduction of the BMD. The degree of heterogeneity was evaluated with the I^2 statistic. We treated the heterogeneity as high when $I^2 \geq 50\%$. A fixed-effect model was conducted when $I^2 < 50\%$, and a random-effect model was operated when $I^2 \geq 50\%$. Further subgroup analyses were performed between the incidence of bone fractures and the baseline characteristics. All statistical analyses were performed with STATA (version 12.0, Stata Corporation, College Station, TX, USA).

3 | RESULTS

3.1 | Study characteristics

The literature review process identified 2483 trials of SGLT2 inhibitors. A total of 27 trials that enrolled 20 895 patients were eligible and included in this meta-analysis. The PRISMA flow diagram is shown in Appendix 2.

The types of SGLT2 inhibitors used in these trials were as follows: dapagliflozin (eight studies, 29.63%), canagliflozin (seven studies, 25.93%), ertugliflozin (four studies, 14.81%), empagliflozin (seven studies, 25.93%), and ipragliflozin (one study, 3.70%). Fracture events occurred in 211 (1.55%) participants in the SGLT2 inhibitor groups (13581 in total) and 108 (1.48%) participants in the placebo groups (7314 in total). Most of the studies were multicountry and multicentre trials, but three trials originated from Japan[20-22] and one trial was from Korea and China.[23] In addition, two studies from Japan lacked clinical trial numbers,[10,21] and one trial from ClinicalTrials.gov had not been published.[24] Two trials were excluded because the participants took pioglitazone as the background therapy.[25,26] The application of TZD had an exact encouraging effect on the occurrence of bone fractures.[7,15] The main characteristics of the included trials are presented in Table 1.

The trial durations ranged from 24 to 206 weeks, with an average of 64.22 weeks. A total of 19 (70.37%) trials had a duration greater than or equal to 52 weeks, and 8 (29.63%) trials had a duration less than 52 weeks. In seven (25.93%) trials included in the meta-analysis, the participants in the same trial did not accept identical background therapy, and we collectively referred to these therapies as antihyperglycaemic agents (AHAs). Baseline characteristics, including age, sex, HbA1c, BMI, and duration of T2DM, were expressed as the mean (SD). In the 27 included trials, the mean age was greater than or equal to 60 years in 11 (40.74%) trials and less than 60 years in 16 (59.26%) trials, and the HbA1c was greater than or equal to 8% in 20 (74.08%) trials, less than 8% in 6 (22.22%) trials, and 1 (3.70%) trial lacked mean HbA1c data. The mean duration of T2DM varied from 4.9 to 16.9 years, representing different stages of T2DM. The numbers of fractures were recorded in both the placebo and SGLT2 inhibitor groups. Some biochemical indicators were also abstracted but not displayed in the article for brevity, such as the BP, serum uric acid (UA), and eGFR level.

3.2 | Quality assessment

The risk of bias of the included trials is summarized in Appendix 3. Most trials showed a low risk of selection, detection, and attrition bias. One trial created a 36-week open extension period,[20] and another trial

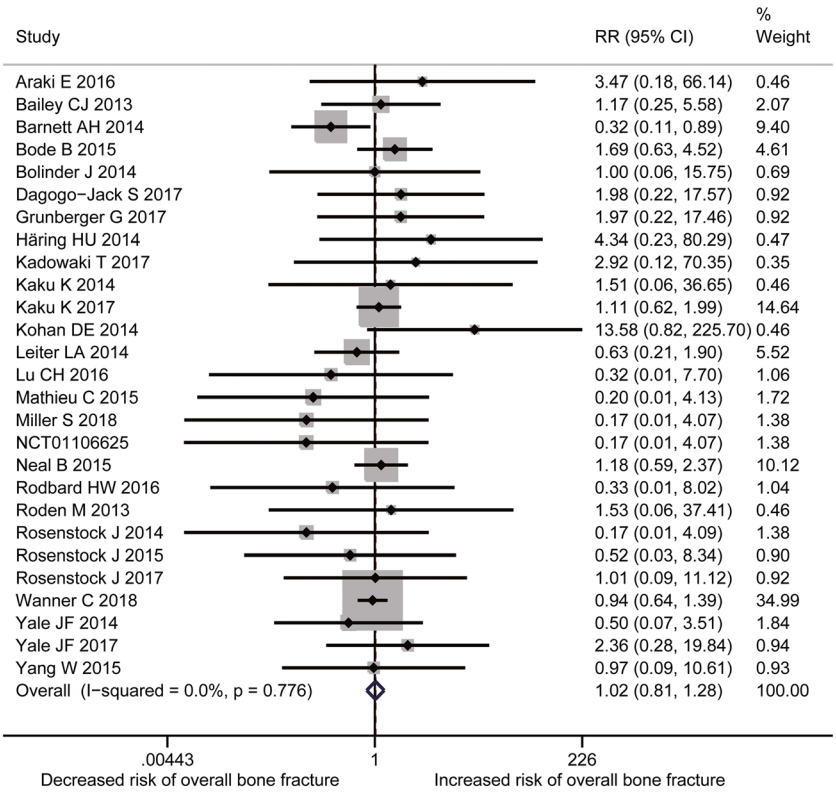

FIGURE 1 The forest plot of relative risk (RR) (95% CI) comparing bone fracture risk in SGLT2 inhibitors treated type 2 diabetes mellitus patients with those treated with a placebo. SGLT2, sodium glucose cotransporter 2

that was only blinded to the patients during the extension period showed a relatively high risk of bias.[27] Reporting bias and other bias were unclear because of a paucity of comprehensive data. When publication bias was evaluated, the funnel plot was visually symmetric and did not provide any evidence of prominent publication bias (Appendix 4). In addition, quantitative analysis of Egger test (0.886) yielded no evidence of significant publication bias.

3.3 | Effect of SGLT2 inhibitors on fractures

Based on the trials included in this meta-analysis, SGLT2 inhibitor therapy did not increase the risk of bone fracture (overall RR = 1.02, 95% CI [0.81, 1.28]), as shown in Figure 1. The pooled RR analysis presented low heterogeneity (I^2 = 0.0%), and a fixed-effect model was conducted.

In the subgroup analysis, we considered the effect of the SGLT2 inhibitor type, dosage, trial duration, background therapy, and some biochemical indexes on bone fracture (Figure 2). The pooled RRs for dapagliflozin, canagliflozin, empagliflozin, and ertugliflozin were 1.33 (95% CI [0.70, 2.51]), 1.21 (95% CI [0.74, 1.97]), 0.89 (95% CI [0.67, 1.20]), and 1.16 (95% CI [0.39, 3.49]), respectively. Different SGLT2 inhibitor dosages were detected, and no influence was found on bone fractures. Ipragliflozin and dapagliflozin at 2.5 mg/day were excluded from the analysis because only one study used these doses. No

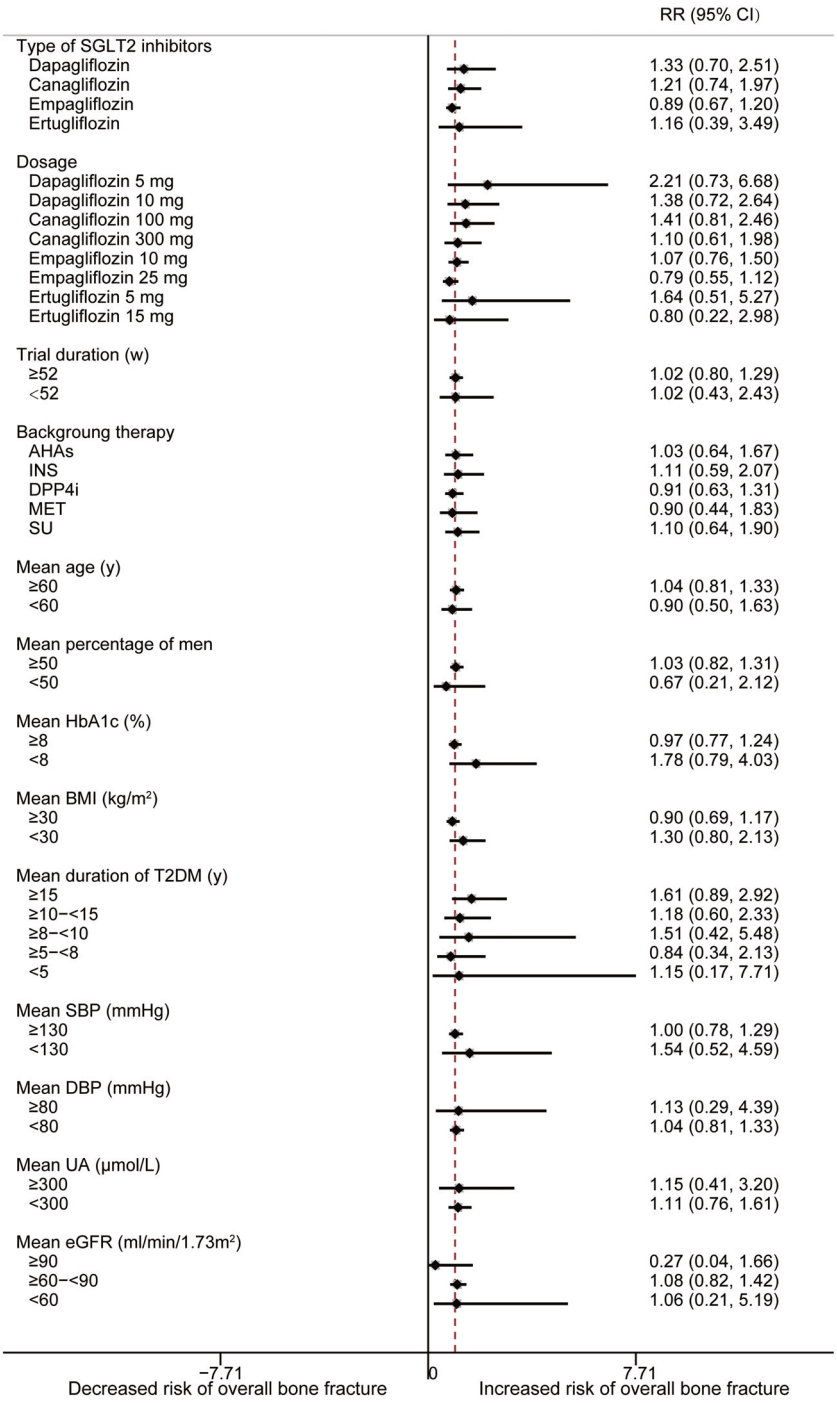

FIGURE 2 Subgroup pairwise meta-analysis of effects of SGLT2 inhibitors on the risk of bone fracture. SGLT2, sodium glucose cotransporter 2; BMI, body mass index; HbA1c, glycosylated haemoglobin A1c; T2DM, type 2 diabetes mellitus; AHAs, antihyperglycaemic agents; INS, insulin; DPP4i, dipeptidyl peptidase IV inhibitors; MET, metformin; SU, sulfonylurea; SBP, systolic blood pressure; DBP, diastolic blood pressure; UA, serum uric acid; eGFR, estimated glomerular filtration rate

correlation was found between a high risk of bone fracture and SGLT2 inhibitor therapy among the subgroup analyses for the trial duration, age, BMI, sex, HbA1c, and T2DM duration. SGLT2 inhibitors did not increase the risk of bone fracture when combined with insulin, DPP4 inhibitors, MET, SU, or other AHAs. Moreover, the SBP, DBP, UA, and eGFR levels did not affect bone health, indicating the relative safety of SGLT2 inhibitors for bone health in patients with impaired BP and renal function. Based on the heterogeneity analysis results, a fixed-effect model was chosen for the review except for the eGFR. All of the results showed that SGLT2 inhibitors did not increase the risk of bone fracture in patients with T2DM.

3.4 | Effect of SGLT2 inhibitors on the BMD

Can SGLT2 inhibitor therapy decrease the BMD but not lead to bone fracture? Three trials were included to reveal changes in the BMD from baseline during SGLT2 inhibitor therapy. Bolinder et al[27] included participants on 10 mg/day of dapagliflozin for 102 weeks; Bilezikian et al[28] used 100 and 300 mg/day of canagliflozin for 104 weeks, and Rosenstock et al[29] used 5 and 15 mg/day of ertugliflozin for 26 weeks (Table 2). The percentage changes in the BMD from baseline in the lumbar spine, femoral neck, total hip, and distal forearm were examined in this meta-analysis. When we focused on the skeletal sites, the BMDs of the lumbar spine were not decreased, but those of the femoral neck, total hip, and distal forearm were significantly impaired. Compared with those of the placebo groups, the BMDs in the SGLT2 inhibitor groups did not show significant changes (lumbar spine WMD = −0.04, 95% CI [−0.43, 0.35], femoral neck WMD = 0.29, 95% CI [−0.13, 0.71], total hip WMD = 0.18, 95% CI [−0.09, 0.45], and distal forearm WMD = −0.20, 95% CI [−0.60, 0.20]) (Figure 3). Based on the existing trials, SGLT2 inhibitors seemed to have no effects on the BMD and bone health. However, on account of the data insufficiency (only three trials), drawing firmer conclusions was difficult.

4 | DISCUSSION

Since the bone health problem of SGLT2 inhibitors was first detected, several possible mechanisms for a higher fracture risk were put forward. However, the mechanisms underlying the association between SGLT2 inhibitor therapy and bone fracture have not been fully elucidated. First, SGLT2 inhibitors disturb calcium homeostasis by acting on SGLT2 in the apical membrane of renal proximal tubules, which is necessary for maintenance of bone health. Second, SGLT2 inhibitors promote reabsorption of phosphate, which increases the plasma fibroblast growth factor 23 (FGF23) levels. Elevated FGF23 leads to an increase in the plasma parathyroid hormone (PTH) levels and a decrease in the plasma $1,25(OH)_2D$ levels. Changes in $1,25(OH)_2D$ and PTH would be pernicious for bone health and ultimately lead to more bone fractures.[16,30] Third, with the obvious adverse action of postural or orthostatic hypotension induced by the reduced intravascular volume, patients receiving SGLT2 inhibitor therapy suffer a greater chance of falls, which obviously leads to more bone fractures.[3]

TABLE 2 Characteristics of included trials on sodium glucose cotransporter 2 (SGLT2) inhibitors and changes in the BMD from baseline

Clinical Trial No.	Author Year	Population	Control (n)	SGLT2 Inhibitors (n)	Background Therapy	Trial Duration, wk		Percent Change in BMD from Baseline				
								Lumbar Spine	Distal Forearm	Femoral Neck	Total Hip	
NCT00855166	Bolinder 2014[27]	Multicountry	PLA (71)	DAP 10 mg (68)	MET	102	Control	0.5 (3.3)	NR	0.1 (3.9)	−0.4 (2.7)	
							SGLT2i	0.7 (3.8)	NR	−0.9 (4.2)	−0.8 (2.9)	
NCT01106651	Bilezikian 2016[28]	Multicountry	PLA (185)	CAN 100 mg (206), 300 mg (192)	AHAs	104	Control	0.5 (4.1)	−0.5 (4.1)	−1.0 (4.1)	−0.5 (0.2)	
							SGLT2i	0.7 (4.3), 0.2 (4.2)	−0.7 (4.3), −0.8 (4.2)	−0.7 (4.3), −0.6 (4.2)	−0.9 (2.9), −1.0 (2.8)	
NCT02033889	Rosenstock 2017[29]	Multicentre	PLA (191)	ERT 5 mg (200), 15 mg (190)	AHAs	26	Control	0.2 (2.9)	0.1 (3.0)	−0.4 (3.3)	−0.6 (2.0)	
							SGLT2i	0.0 (3.2), 0.2 (2.9)	−0.1 (2.7), −0.1 (2.8)	−0.1 (3.2), 0.3 (3.8)	−0.5 (2.0), −0.4 (2.2)	

Note. Data are mean (SD) unless otherwise indicated.

Abbreviations: SGLT2i, sodium glucose cotransporter 2 inhibitors; BMD, bone mineral density; PLA, placebo; NR, not reported; MET, metformin; AHAs, antihyperglycaemic agents; DAP, dapagliflozin; CAN, canagliflozin; ERT, ertugliflozin.

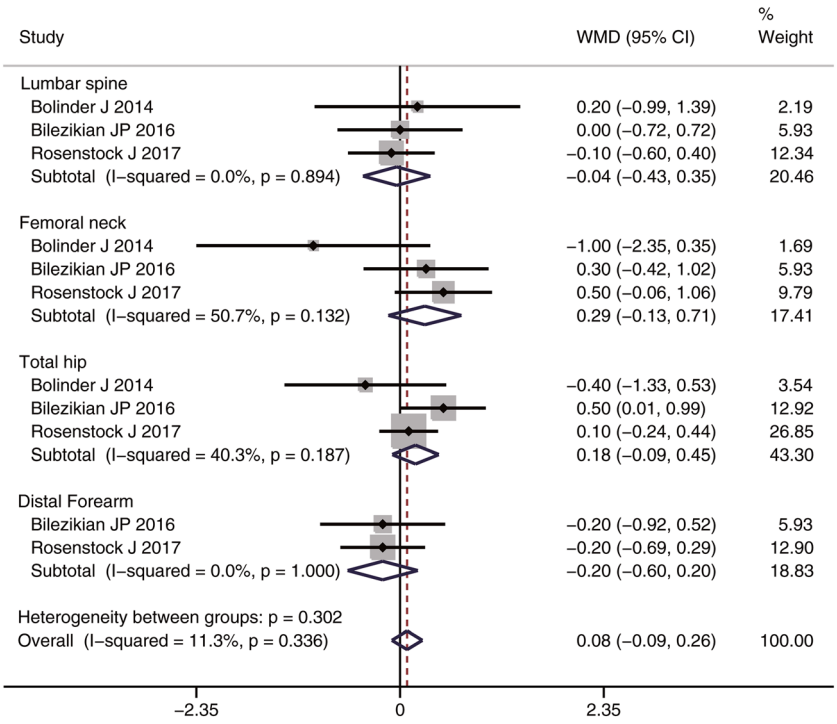

FIGURE 3 The forest plot of WMD (95% CI) of changes in bone mineral density from baseline, comparing SGLT2 inhibitors treated type 2 diabetes mellitus patients with those treated with placebo. WMD, weighted mean difference. SGLT2, sodium glucose cotransporter 2

In preclinical studies, no decrease in the BMD was found in rats treated with SGLT2 inhibitors. SGLT2 inhibitors affected neither bone formation nor bone resorption in vivo and played a neutral or a potential positive role in the bone.[7] Whether SGLT2 inhibitors give rise to a higher risk of bone fracture has received equal attention in clinical practice. Two previous meta-analyses did not find a correlation between SGLT2 inhibitor therapy and a higher risk of fracture.[13,14] Ruanpeng et al retrieved 20 studies on canagliflozin, dapagliflozin, and empagliflozin.[14] This study included 8286 patients from inception to November 2015 and did not observe an increased risk of bone fracture among patients with T2DM. The other meta-analysis compared the effects of SGLT2 inhibitors (canagliflozin, dapagliflozin, and empagliflozin) with a placebo or other active antidiabetic treatments on bone fracture.[13] Thirty-eight eligible RCTs with 30 384 patients were involved from inception to January 2016, but the study lacked evidence of the harmful effect of SGLT2 inhibitors on fracture. In 2018, Kohler et al analysed the fracture risk in empagliflozin-treated diabetics with pooled data, and bone fractures were reported in 2.8%, 2.5%, and 2.9% patients in the empagliflozin 10 mg, empagliflozin 25 mg, and placebo groups, respectively.[31] However, all of the reviews lacked details on bone health outcomes, and most trials were short-term studies. More long-term and eligible trials need to be included, and the effects of SGLT2 inhibitors on fracture in patients with T2DM need to be updated.

This study reviewed 27 RCTs on dapagliflozin, canagliflozin, ertugliflozin, empagliflozin, and ipragliflozin with a placebo that enrolled 20 895 patients with T2DM from inception to March 2018. Compared with those of previous reviews, our meta-analysis has several advantages. (1) More long-term trials were included. The included trials ranged from 24 to 206 weeks, with an average of 64.22 weeks; thus, the duration of the trials included in this meta-analysis was longer than that of the previous two studies (Ruanpeng et al[14] 24 to 104 weeks, average 38 weeks and Tang et al[13] 24 to 160 weeks, average 57.47 weeks). (2) This analysis was based on the latest research. This meta-analysis included clinical trials from inception to March 2018, which prolonged the cut-off time of retrieval and obtained the latest studies. (3) We applied unitary comparison methods. We restricted the control group to placebo treatment rather than comparing SGLT2 inhibitors to a placebo or other active antidiabetic treatments. This approach allowed us to rule out interference from other positive drugs. (4) We used a more objective evaluation index. We not only reviewed the incidence of bone fracture but also analysed changes in the BMD, which is an objective indicator of bone health. (5) High-quality evidence was included. The inclusion criteria for this meta-analysis were restricted to RCTs. As the most reliable clinical evidence, RCTs provide more reliable data sources.

Theoretically, SGLT2 inhibitors might contribute to a greater risk of bone fracture, but the findings did not meet the results of our and previous meta-analyses.[13,14] First, bone fractures are greatly affected by external factors, such as traffic accidents. A certain degree of external force can contribute to bone fracture even though SGLT2 inhibitors do not affect bone health. Second, diabetic complications also affect bone fracture. Diabetic neuropathy, diabetic retinopathy, and hypoglycaemic events would increase the risk of falling and thus the risk of bone fracture.[2]

Aside from the external and internal interference factors mentioned above, some limitations still affected the results of our meta-analysis. The impact of SGLT2 inhibitors is a long-term process. Although the duration of the included trials was dramatically prolonged, it still might not be sufficient to evaluate the long-term effect of SGLT2 inhibitors on bone health. In addition, seven of the included trials did not limit the background therapy to identical

treatments and were represented by AHA therapy.[5,32,33,34,35,36,37] Different background therapy may reduce reliability in trials.

Many biochemical markers reflect the changes in bone metabolism, such as C-terminal cross-linking telopeptide (CTX), N-terminal cross-linking telopeptide (NTX), bone-specific alkaline phosphatase (BAP), parathyroid hormone (PTH), and 25-OH vitamin D. Because these markers definitely represent bone metabolism and bone turnover, reviews of them may provide a more comprehensive and objective analysis of this problem. Furthermore, the trabecular bone score (TBS) is another reliable bone fracture predictor, that is more suitable for indicating the fracture risk in patients with T2DM.[7,38] The TBS is a texture index that is used to evaluate dual-energy X-ray absorptiometry images and the bone microarchitecture independent of the BMD.[39] Unfortunately, most trials only evaluated the bone fracture incidence instead of these biochemical indicators. Therefore, we only analysed the BMD as the quantitative index in this meta-analysis, and we look forward to studies with more objective and proper data.

Recently, another meta-analysis about the risk of bone fracture associated with SGLT2 inhibitor treatment was published.[40] The pooled odds ratio (OR) of bone fracture was 0.86 (95% CI [0.70, 1.06]), and no increased risk was detected. However, Cheng et al only analysed different types and doses of SGLT2 inhibitors, along with different treatment durations in subgroup analyses. We not only analysed types, dosages, and treatment durations but also background therapies, ages, sexes, BMIs, durations of T2DM, and other biochemical indexes of BP or renal function. Moreover, changes in the BMD from baseline were analysed in our research, which was ignored by the previous three meta-analyses.[13,14,40] The monitoring of the changes of BMD is more sensitive and objective to reveal slight effects.

As an increasingly recognized complication of T2DM, the bone fragility problem should receive more attention. Based on the new algorithm of bone health in diabetics published by the Bone and Diabetes Working Group of the International Osteoporosis Foundation,[38] a BMD *T* score less than −2.5 in postmenopausal women and men over 50 years of age confirms the diagnosis of osteoporosis and indicates a need to consider pharmacotherapy. However, a BMD *T* score less than −2 at the spine or hip in diabetics should be measured as the threshold. When assessing the fracture risk with FRAX, rheumatoid arthritis (RA) should be substituted for T2DM to capture the excess risk. Based on existing trials, SGLT2 inhibitor treatments neither increased the risk of bone fracture nor decreased the BMD compared with that of the placebos. However, given that bone health damage is a relatively long-term process and may be affected by several external factors, SGLT2 inhibitors may not have adverse effects on bone health, but more long-term detailed data are needed to validate this conclusion.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest associated with this manuscript.

AUTHOR CONTRIBUTIONS

X. Y. L., B. S., and L. M. C. conceived and designed this study. X. Y. L., T. L., Y. C., and Y. H. L. collected and analysed the data and revised by M. X., L. X. X., X. Y. L., and X. C. Y.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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